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Review

Sleep, epilepsy, and autism

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ABSTRACT

The purpose of this review article is to explore the links between sleep and epilepsy and the treatment of sleep problems in children with autism spectrum disorder (ASD). Epilepsy and sleep have bidirectional relationships, and problems with both are highly prevalent in children with ASD. Literature is reviewed to support the view that sleep is particularly important to address in the context of ASD. Identification and management of sleep disorders may improve seizure control and challenging behaviors. In closing, special considerations for evaluating and treating sleep disorders in children with ASD and epilepsy are reviewed.

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1. Introduction

Sleep is a complex dance of closely coordinated physiologic processes, resulting in a state of consciousness in which we spend a large amount of our lives. Sleep has an architecture in terms of orderly progression through stages of nonrapid eye movement (NREM) and rapid eye movement (REM) sleep. It also has rhythms influenced by internal circadian clocks and external environmental stimuli such as light. Sleep medicine is a relatively young field of study pioneered by Nathaniel Kleitman and Eugene Aserinsky in the 1960s with the advent of modern polysomnography [1]. Despite the extraordinary degree to which sleep is evolutionarily conserved, its purpose is not yet well understood [2]. Synaptic plasticity has been hypothesized as a reason for sleep [3].

2. Intersection of sleep and epilepsy

Sleep deprivation has long been recognized as responsible for lowering seizure thresholds in persons with epilepsy. Acute sleep deprivation causes a rebound increase in the stage of sleep known as N3 or slow-wave sleep. Slow-wave sleep, defined by high-amplitude slow-frequency EEG, is the most highly synchronized sleep stage; its slow thalamocortical oscillations may be closely associated with epileptogenesis [4,5]. Many varieties of epilepsy have seizures that occur primarily or exclusively during sleep.

Sleep deprivation can be voluntary or involuntary. Sleep is vulnerable to its own unique set of disorders that can disrupt it. Among these are sleep-related breathing disorders. Obstructive sleep apnea (OSA) is one such disorder, which often manifests with snoring or difficulties in breathing, characterized by transient, intermittent respiratory obstructions unique to sleep. Obstruction is more frequent and problematic during REM sleep because of relative muscle atonia. Obstructive sleep apnea can result in sleep fragmentation and oxygen desaturations.

Obstructive sleep apnea is not at all uncommon among typically developing children, with a baseline prevalence of 1–3% and increased risks among Black children and former preterm infants [6,7]. In adults with epilepsy, the risk of OSA increases with higher doses of antiepileptic drugs (AEDs) [8]. In children with epilepsy, adding more than one AED also increases the risk of OSA [9]. In addition, adults with refractory epilepsy are at higher risk of OSA, with 33% of them meeting the criteria on the basis of polysomnography (PSG) [10]. Children with refractory epilepsy have had more symptoms of OSA reported, i.e., 44% vs. 31% for milder epilepsy [9]. Treatment of OSA can improve seizure control, sometimes to a striking degree [11–14].

However, not only does sleep – or lack thereof – affect epilepsy, but epilepsy, in turn, also affects sleep. People with epilepsy have more prevalent sleep disorder diagnoses, and adults have lower self-rated quality of sleep. Children with poorly controlled seizures show less efficient sleep (more time awake in bed), more frequent arousals from sleep, and higher percentages of REM sleep compared with children

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with well-controlled seizures or without epilepsy [15]. Paradoxically, these children may also have higher percentages of REM sleep, perhaps as a protective mechanism (as REM sleep is a relatively antiepileptic state). This bidirectional relationship challenges our understanding of both sleep and epilepsy.

3. Sleep in children with autism

Children spend a larger percentage of their lives in sleep compared with adults, strengthening the case for sleep's importance to the developing brain. Sleep disturbance in children with autism spectrum disorder (ASD), who may be least able to tolerate lack of sleep, is distressingly prevalent, with estimates ranging from 40 to 80% of children affected [16]. Sleep issues are common among typically developing children as well but likely more common and more intense in children with ASD. In general, sleep disorders can be characterized in the broad categories of too little sleep, too much sleep, unusual activities during or around sleep, and sleep at inappropriate times. Children with ASD overwhelmingly struggle with insomnia, defined as a sleep disorder that is characterized by difficulty falling asleep and/or maintaining sleep, which is nonrestorative, in some fashion [17].

However, other sleep disorders have been documented among children with ASD. While OSA may not affect children with ASD more frequently than the pediatric population, some children with ASD are likely to be affected. Use of atypical antipsychotic drugs such as risperidone to moderate behaviors can cause substantial weight gain, likely placing children at higher risk of OSA. In one case report, treatment of children with OSA and ASD improved but not completely resolved symptoms of autism [18].

Parasomnias (e.g., confusional arousals, night terrors, and sleepwalking) are quite common in typically developing children. Parasomnias represent mixed states with characteristics of both sleep and wake, most often occurring out of slow-wave sleep. These have the potential for disrupting sleep or a child's household. Their frequency in children with ASD is unknown, but they are likely underdiagnosed, as parents can have difficulty ascertaining whether a child who is moving about or distressed during the night is fully awake [19]. Atypical parasomnias can be confused with seizures and may require video-EEG and PSG [20].

Researchers have begun to question whether conditions such as restless legs syndrome (RLS) and circadian rhythm sleep disorders may also affect more children with ASD than commonly recognized, as communication issues in autism pose diagnostic challenges [21]. Restless legs syndrome is diagnosed based on clinical history, a history many children would find it difficult to provide [22]. Periodic limb movements (PLMS) as recorded on PSG can provide objective supportive evidence for disorders on the RLS/periodic limb movement disorder (PLMD) continuum [23]. Periodic limb movements can also contribute to fragmented sleep. Low serum ferritin, a marker for iron stores, often serves as a marker for potential benefit to sleep for iron supplementation [24]. Evidence whether children with ASD have lower serum ferritin compared with typically developing peers is mixed, but it seems that children with lower ferritin may benefit from iron supplementation [25,26]. Use of certain medications, including the commonly used selective serotonin reuptake inhibitors, can also provoke PLMSs, potentially leading to sleep fragmentation [27]. Circadian rhythm sleep disorders are often suspected in children with ASD but can be difficult to document. Significantly delayed sleep onset and unusual sleep schedules are certainly suggestive. Melatonin is a hormone whose secretion contributes to the regulation of the sleep–wake cycle. Some past measures of melatonin metabolites in children with ASD showed abnormalities, but patterns of endogenous melatonin secretion during sleep in ASD may actually be relatively normal [28].

Sleep deprivation has well-documented consequences for learning, mood, and behavior among adults and children [29]. Sleep disruption affects not only children but also their families, as, often, parents stay awake to supervise their children with delayed sleep and night wakings [30]. Significant behavioral gains can result from treatment of sleep. Sleep has, therefore, gained attention as a potentially modifiable factor that could improve daytime neurobehavioral function, not to mention family quality of life.

4. Sleep and epilepsy in autism

Autism used to be considered a psychological reaction to a chilly parenting style; this unpleasant theory was challenged by the unavoidable fact that a significant percentage of children with ASD have epilepsy, which is, clearly, a brain-based disorder [31]. As many as 30% or more of people with ASD have some EEG abnormalities or have clinical seizures [32]. Electrical status epilepticus of sleep (ESES) is one consideration for children with ASD. This nonspecific term refers to any increase in epileptic discharges during sleep, potentially applicable to Landau–Kleffner syndrome, atypical rolandic epilepsy, and continuous spikes and waves during sleep (CSWS). Slow-wave sleep provokes frequent, bilateral 1.5- to 3-Hz spike–wave complexes [33]. These children often have symptomatic epilepsy with identifiable causes; the majority have clinically apparent seizures as well as developmental disorders during the day. Electrical status epilepticus of sleep, however, has been associated with developmental regression. Current practice parameters prompt clinicians to consider EEG depending on history or physical findings [34].

Collectively, single gene, microdeletion, microduplication, and translocation syndromes are recognized as causative in about 10% of cases of ASD, a diagnosis which itself carries an increased risk of epilepsy [35]. Tuberous sclerosis complex (TSC), a single gene disorder, affects not only multiple organ systems but also neuronal connectivity, resulting in highly prevalent autism, seizures, and sleep issues [36]. Its genetic and pathophysiologic pathways have been proposed as a model for autism. Mechanism-based treatments currently studied for associated seizures are being evaluated in terms of effects on sleep as well as seizures [36]. The chromosomal duplication syndrome 15q isodicentric duplication may be the most common copy number variant associated with autism [37]. Reports of sudden unexpected death in epilepsy (SUDEP) have been published for children with this duplication [37]. De novo copy number variations such as 16p11.2 deletion and 15q13.3 deletion or duplication can also present with ASD [35,38] and manifest with seizures [39,40]. Mouse models of 16p11.2 deletion show differences in diurnal activity level consistent with sleep problems [41].

A major clinical challenge is how to approach the child with ASD who has disrupted nighttime sleep and EEG abnormalities without a history of clinical seizures. Even a large retrospective analysis of otherwise healthy children undergoing PSG revealed 1.45% with epileptiform discharges on limited EEG, so they are not uncommon [42]. Interictal spikes during REM sleep can interrupt theta activity and hippocampal and entorhinal oscillations which register and consolidate memories [43]. Similarly, interictal spikes during slow-wave sleep also interfere with consolidation of memories [43]. The mantra of the classically trained child neurologist is to “treat the child, not the EEG,” and the treatment of interictal spikes has been controversial at best [44]. However, the degree of distress associated with limited sleep and our sometimes limited treatment palette may prompt empiric trials of AEDs with the goal of increased sleep duration or quality.

5. Evaluations

Clinicians both underrecognize and misidentify sleep disorders in children with epilepsy [45]. Attention to history and appropriate use of diagnostic tools can ensure correct diagnosis. Taking a sleep-oriented history narrows down what kind of sleep disorders may be at work. How long has sleep been an issue? Does the child have difficulty falling asleep, staying asleep, or both? Does he resist going to bed, or awaken extra early? Do parents question whether sleep is restful, based on excessive movement during sleep, sleep talking, bruxism, or crying? Is the child excessively sleepy during the day or on an

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irregular schedule with lots of napping? Does the child snore or have noisy breathing? Has she had any witnessed apneas? Witnessed apneas, however, are not required for the clinician to suspect or further investigate sleep-disordered breathing. How does sleep disruption affect the child? Some children have marked impairment after a rough night's sleep; others seem to take this in stride. Also, how does sleep disruption affect the rest of the family? Parents of children whose sleep is disrupted often stay up late or wake during the night to supervise their children.

Use of questionnaires such as the Children's Sleep Habits Questionnaire (CSHQ), Family Inventory of Sleep Habits (FISH), or Pediatric Sleep Questionnaire (PSQ), each of which screens somewhat different sleep issues, can provide more structured information and opportunity for comparison with specific cutoff scores [46]. The CSHQ was originally developed for 4–10 year olds, though its use has been extended down to 2 years old and up to 18 years old within the national Autism Treatment Network. Its questions focus on categories of common sleep disturbance in children, with categories such as bedtime resistance, sleep anxiety, parasomnias, and daytime sleepiness. The FISH was developed specifically for children with ASD to identify dysfunctional sleep habits and environments ("sleep hygiene") and validated in 4- to 10-year-old children with ASD and in those without ASD [47]. The PSQ has subscales designed to identify 2- to 18-year-old children with sleep-disordered breathing and periodic limb movements during sleep, which have been validated against PSG [48,49].

Cosleeping is common, but parents are often embarrassed about discussing it. It probably persists longer in children with disabilities such as ASD who resist change and may have delays in becoming independent in many areas of function. It is also more frequent among children with epilepsy, as parents may be anxious about missing nighttime seizures and want to be immediately available for emergencies [50]. Discussing cosleeping is important in order to gauge parental worry, especially about consequences of seizures.

Tonsillar hypertrophy, receding jaw and "adenoidal facies" (long, slack-appearing face with open mouth), can suggest obstructive sleep apnea, though are not guarantees of this condition. Oropharyngeal crowding in particular does not equate to obstruction. Likewise, hypotonia and obesity increase the risk of sleep-disordered breathing. History and physical examination cannot definitively diagnose obstructive sleep apnea [51].

Overnight PSG or, more colloquially, an overnight sleep study is the gold standard test to assess breathing during sleep [52]. Obstructive sleep apnea affects 1–3% of children [6]. It can also measure periodic limb movements, a kind of repetitive leg movement. The presence of periodic limb movements can constitute a diagnosis of PLMD or support a diagnosis of RLS. Importantly, though, RLS cannot be diagnosed with PSG: it is a clinical diagnosis which is challenging to make in children with communication limitations. The American Academy of Sleep Medicine guidelines for pediatric PSG recommend clinical screening for comorbid sleep disorders for children with epilepsy and performance of PSG if breathing issues or PLMD is suspected [53]. In addition, the same guidelines offer the use of PSG with expanded EEG montage as an option in children in whom symptoms raise the question of parasomnia vs. epilepsy [53]. An extended 10–20 montage EEG during PSG is probably underused, especially given the significant overlap between epilepsy and sleep disorders [54]. Polysomnography is not trivial to perform on children with ASD: although considered noninvasive, PSG, nonetheless, requires cooperation with monitoring and tolerance of numerous unfamiliar sensations. However, a thoughtful approach to the needs of children and families, as well as preparation when available, can ease the stress of this procedure [55].

Quantitative EEG (qEEG) and analysis of cyclic alternating pattern (CAP) sequences present alternative ways to examine sleep in children with autism. These methods are primarily used on a research basis, rather than clinically. With qEEG, power spectral analysis (PSA) calculates multiple metrics: bands of delta, theta, alpha, and beta frequencies. This technique can objectively characterize rather than qualitatively describe coherence of power spectra during sleep, which is often atypical among people with brain-based disorders such as ASD [56]. Another qEEG method, detrended function analysis (DFA), generates a single metric called the scaling exponent that better compensates for artifact and takes into account the nonlinear nature of EEG data [57]. Algorithms to quantify nonlinear features have shown significant differences between ictal and interictal EEGs [58]. Power spectral analysis and DFA have correlated in adults with sleepiness and neurobehavioral changes, with potential intriguing applications among children with ASD [57]. Quantifying CAP sequences, elements of sleep microarchitecture indicative of sleep instability which occur during non-REM sleep, may offer novel insights into the disruption of sleep in children with ASD [59]. A CAP sequence involves an A phase followed by a B phase: the A phase consists of high-amplitude slow EEG waves, while the B phase consists of low-amplitude, irregular EEG activity [59] Sequences are graded on degree of EEG desynchrony. There are published normal values available for their rate of occurrence at different ages. While differences in CAP are not pathognomonic for ASD, decreases in CAP rate have characterized sleep-disordered breathing, parasomnias, and a variety of neurodevelopmental disabilities [60].

Actigraphy detects and records movement over time as a proxy for sleep and wake. Actigrams are typically worn as wristwatch-like devices on the nondominant hand, although placement on the ankle and even on the shoulder has been used, especially in children with sensory sensitivities [61,62]. Downloads of activity records over a period of days can reveal patterns of sleep–wake which may be useful clinically. In particular, wakings after parents have gone to sleep can be better characterized in frequency and duration.

6. Issues in treatment

The Autism Speaks Autism Treatment Network, in collaboration with the National Initiative for Children's Healthcare Quality, has developed practice parameters for the evaluation and treatment of insomnia in children with ASD [63]. Following assessment for medical comorbidities (including epilepsy), the first line of treatment recommended is behavioral [63]. However, acknowledging that not all families are able to embark on a consistent program of behavior modification, pharmacologic treatment of sleep is also an option [61].

The United States Food and Drug Administration has not approved any medications for insomnia for use in children. Clonidine, mirtazapine, and risperidone have all been used, with limited data on efficacy available [63].

Melatonin is a hormone which regulates sleep–wake cycles. It is sold as an over-the-counter dietary supplement. It is inexpensive and widely available. In the past, it has been classified as a complementary medicine. It has a generally good safety record. Several small randomized controlled trials have shown that it can increase sleep time in children with ASD [64]. In a large retrospective study, [65], short-term side effects were generally mild, although data on long-term effects are lacking. Cross-sectional data in the Interactive Autism Network (IAN), a pioneering online study which has collected information on ~15,000 subjects with ASD, show that >10% of children with treatment information use melatonin (unpublished data).

Many medications with potential clinical applications in children with ASD have sedating effects. Gabapentin and pregabalin have both antiepileptic and sedating effects, and evidence for use of gabapentin for sleep maintenance in children with ASD is emerging [66]. Conversely, sedating AEDs may add to the sleepiness caused by unidentified sleep disorders such as OSA. Antidepressants such as amitriptyline, doxepin, trazodone, and mirtazapine may promote sleep by increasing total sleep time, decreasing sleep-onset latency, or increasing slow-wave sleep, but sleep effects are not well studied [67]. Most antidepressants are also powerful REM sleep suppressors.

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Some AEDs, such as valproic acid and lamotrigine, may also act as mood stabilizers that can have additional behavioral benefits. Levetiracetam is a highly effective AED that, conversely, can result in irritability that can limit its usefulness in children with ASD who already have behavioral dysregulation. Risperidone and other atypical antipsychotic medications have been used to moderate behavioral challenges in children with ASD; they may affect sleep both directly through sedative effects or more indirectly through significant weight gain potentiating obstructive sleep apnea [68].

Vagus nerve stimulator (VNS) treatment is a novel adjunct treatment sometimes reserved for refractory epilepsy, as it is rarely curative. This surgically implanted device stimulates the vagus nerve at a preset frequency, and its antiepileptic mechanism is not entirely clear. Treatment with VNS has been associated with obstructive sleep apnea [69,70]. It should be approached with caution in patients who already have symptoms of sleep-disordered breathing. There have been concerns about melatonin potentiating seizures [71]. These have not been borne out in more recent clinical series, with no increase in seizure frequency among children with epilepsy placed on melatonin, no incidence of new seizure types, and no occurrence of new-onset seizures [65,72]. In fact, melatonin may actually have some antiepileptic as well as chronobiotic effects [73].

There is much work to be done in the field of autism, sleep, and epilepsy. Dissemination of existing indications for the evaluation and treatment of sleep issues and potential benefits for seizure control is a first step. More precise diagnosis of sleep disorders can guide treatment more accurately. Developing more effective treatments for sleep disorders in children with ASD, especially evidence-based pharmacologic treatments, will be critical.

Disclosures

The authors have no conflicts of interest to disclose.

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